

# Engineering Devices to Treat Epilepsy: A Clinical Perspective

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**Abstract-** 25% of the world's 50 million people with epilepsy have seizures that cannot be controlled by medication or epilepsy surgery. The need for new therapeutic options is clear. Since the 1970's clinicians, neuroscientists and engineers have proposed technologies for treating seizures, with the ultimate goal of implanting stimulators or drug infusion devices in brain to abort seizures before clinical onset. Interest in the field has exploded in recent years, due to evidence suggesting that seizures may be predictable. Device designs range from "blind" stimulators, which do not respond to physiological activity, to "intelligent" devices, which are triggered by detecting or predicting seizure onset. To gain acceptance, intracranial implants will need to demonstrate more than marginal efficacy to justify their invasiveness. Unlike their cardiology predecessors, intelligent implantable epilepsy devices will likely process multiple channels of data, be tuned to individual patients and may need to predict events rather than detect them, for maximal effectiveness. Carefully designed clinical trials will be required to perfect and validate the efficacy of implantable devices for epilepsy, before clinical use becomes widespread.

**Keywords** - EEG, epilepsy, implantable devices, seizure prediction, stimulation, infusion

## I. BACKGROUND

As early as 1954, Penfield and Jasper suggested that a central functional structure deep in the brain was responsible for propagating epileptic seizures from discrete, electrically unstable areas, or *foci*, to broad regions of the cerebral cortex [1]. Research over the next three decades reinforced the idea that seizures likely spread through discrete, functional neuronal networks [2].

Over the last 15 years, researchers have demonstrated that it is possible to modulate the activity of functional neuronal networks in animal models of epilepsy by electrical stimulation and localized infusion of antiepileptic drugs. These methods can be used to arrest, suppress or increase resistance to epileptic seizures. Target regions have included central structures, such as the subthalamic nucleus [3], the anterior thalamic nucleus [4], the hypothalamus [5], mamillary bodies [6], cerebellum [7], basal ganglia [8], locus ceruleus [9] and the substantia nigra [10]. At the same time some investigators have demonstrated similar proof of principle by stimulating more peripheral extensions of the central nervous system, such as the vagus nerve in dogs [11] and the trigeminal nerve in rodents [12]. *In-vitro* experiments

in hippocampal slice models of epilepsy, have demonstrated the effectiveness of not only direct electrical stimulation in arresting seizures [13], but also through applying magnetic fields [14] and local cooling coils (Peltier devices) [15]. In addition, seizures have been arrested in animal models of epilepsy through local infusion of antiepileptic drugs into regions generating seizures (epileptic foci) [16]. Though important first steps, these experiments are far removed from demonstrating efficacy in human epilepsy. Sorting out how and where to intervene with electrical stimulation or drug infusion to treat which type(s) of human epilepsy, is one of the major challenges in developing implantable antiepileptic devices.

Based upon this animal literature, beginning in the 1970s, investigators initiated early clinical trials of brain and peripheral nerve stimulation in humans with medically resistant epilepsy. These included trials of cerebellar stimulation [17], centromedian thalamus [18] and periodic hippocampal stimulation [19]. These studies demonstrated that chronic, intracranial electrodes are well tolerated, and encouraging preliminary results. Because of their lack of controls and unblinded design, in most cases, these results have demonstrated sufficient efficacy to support Food and Drug Administration device approval. Two double-blind, controlled trials of brain stimulation for epilepsy published to date have been less encouraging, demonstrating low efficacy for cerebellar [20] and centromedian thalamus stimulation [21]. These studies all used paradigms of intermittent, "blind" stimulation, in which stimulators were turned on and off at regular intervals, independent of the patient's state of awareness or proximity in time to seizures. There are as of yet no authoritative, published positive results of double blind, controlled clinical trials of electrical stimulation on the surface or in the substance of the brain for intractable epilepsy.

The vagal nerve stimulator (VNS) is the first implantable medical device approved by the FDA for the treatment of epilepsy. This device consists of an implantable, pacemaker-like stimulation unit implanted under the clavicle, connected to an electrode wrapped around the vagus nerve on the left side of the neck. The device reduces seizure frequency an average of 20-30% in most individuals, with an approximately 10% chance of being seizure-free [22].

In 1999, Lesser et al. reported that focal electrical stimulation of the cerebral cortex can suppress rhythmic after-discharges provoked by stimulation mapping of cortical function prior to epilepsy surgery via subdural electrodes. In this study, after-discharges were suppressed by short

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duration, bipolar current pulses applied to the electrode contacts generating the after-discharges [23]. This is one of the first studies in man demonstrating the efficacy of reactive or “intelligent” brain stimulation in the region of the epileptic focus as a means of suppressing seizure-like activity in humans. In this case the “intelligence” consisted of a physician, or staff member, recognizing the presence of afterdischarges on the EEG and triggering counter stimulation. While encouraging, these results must be viewed with the understanding that the link between provoked afterdischarges and spontaneous epileptic seizures is at best unclear.

## II. DETECTION, PREDICTION AND CLOSED-LOOP SYSTEMS

Chronic “blind” stimulating devices intended to modulate seizures by activating or inactivating specific network regions remain an active area of research for epilepsy implants, due to their relative simplicity and the success of similar devices for treating symptoms of Parkinson’s disease and tremor. More promising perhaps are reactive, “intelligent” devices, which are activated in response specific patterns of brain activity.

Recent research suggests that epileptic seizures, particularly in the temporal lobe, may begin up to hours prior to their electrical onset [24]. A variety of computational methods have been proposed for measuring these changes, ranging from non-linear dynamics, to linear measures extracted from the EEG, to combinations of multiple parameters [24-28]. These algorithms complement other signal processing methods to rapidly *detect* seizure onset on EEG, which can be used to trigger therapeutic intervention [29, 30]. Exactly how, and in which types of epilepsy these algorithms are best employed remains to be determined. Triggering therapy to seizure detection may be quite useful for epileptic foci in the hippocampus, where seizures may remain confined for up to 10 seconds prior to propagation. Seizures which spread much more rapidly, such as in the frontal lobe, may be much more difficult to approach with this technique, and may require recognition of seizure precursors to first localize epileptic foci in these regions, as well as guide intervention. While some investigators postulate that waiting until electrical seizure onset is detected on EEG may be too late to disrupt clinical seizures, most acknowledge that devices based on seizure detection are likely to be the first generation of implantables for epilepsy. Prediction-based devices are likely to be more complex, requiring multiple input channels to allow spatial sampling of the electrocorticogram, and multiple stimulating electrode sites, in order to disrupt the process of seizure generation. Early evidence suggests that both seizure detection and prediction devices will need to be “tuned” to individual patient patterns, and may require fusion of a number of features extracted from the EEG signal for optimal performance [28]. A schematic for one such implantable device is presented in Figure 1. Incorporating this ability in

the 100 kHz processing environment typical of implantable devices is a formidable engineering challenge.

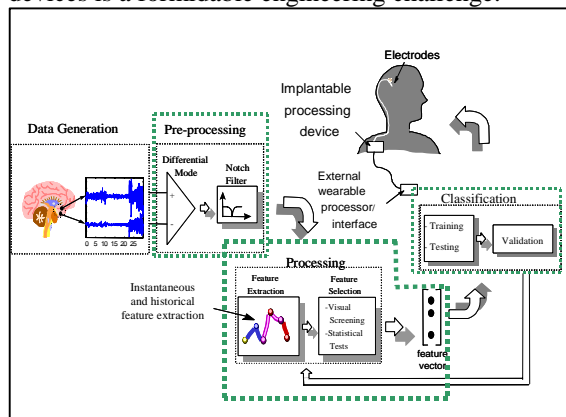


Figure 1: Schematic of “intelligent” epilepsy device, including data acquisition, pre-processing, feature extraction, classification stages.

## III. DIFFERENT FROM CARDIOLOGY DEVICES

As epilepsy devices are developed, it is only natural to look to their cardiology predecessors, particularly implantable cardiac defibrillators (ICDs) for comparison. These devices typically monitor a single channel of the ECG for life-threatening arrhythmia patterns. When such a pattern is detected the device triggers a program of escalating electrical stimulation, which increases in intensity, until arrhythmias are controlled. Side effects can be appreciable, sometimes causing significant discomfort and pain, at higher energies. Patients may lose consciousness or fall to the ground either as a result of decreased blood flow to the brain, since arrhythmias are monitored for unequivocal onset, or as a result of high energy shocks delivered by the device. Since the purpose of these devices is to save lives, such side effects are considered tolerable and are accepted.

Epilepsy devices are both more complex and subject to lower tolerance for side effects than their cardiology analogs. Since their purpose is to prevent seizures and their symptoms, such as loss of awareness, distracting sensations and involuntary movements, side effects such as significant pain and falling are unacceptable. Rather than prevent death, these devices are intended to restore normal life and behavior, such as allowing affected individuals to drive. Error tolerance in event detection will be similarly low, compared to ICDs, as even a single seizure while driving on the highway provides unacceptable risk to many active candidates for such therapy. Different from ICDs, it is less likely that the specific patterns to be recognized by epilepsy devices will be generalizable from one patient to the next. Rather, seizure detection and prediction algorithms are likely to be “tuned” to the individual patterns, for maximal performance. Similar to ICDs, devices based upon seizure detection or prediction will likely contain programs of escalating intervention to broaden

the number of electrode contacts being activated and increase stimulation intensity or change stimulating paradigms, if seizures are not prevented or their spread controlled. In one such scheme, our group has suggested that stimulation intensity and distribution should be guided by estimated probability of seizure onset over time [24]. In this way, mild stimuli can be initiated during periods of low but rising probability of seizure onset. Since these mild stimuli are likely to be relatively benign, they can hopefully be delivered with relative impunity during periods when seizure precursors first begin, where the false positive rate of seizure prediction is high. Similarly, as the probability of seizure onset increases, and stimulation increases in spatial distribution and intensity, false positive predictions must also decline in a similar fashion. This is but one potential therapeutic scheme of many, which could be employed to control implantable devices for epilepsy.

#### IV. TRIALS AND VALIDATION

The most prudent way of translating research on seizure detection, prediction and intervention for implantable devices into the clinical realm is not clear. The burgeoning clinical need for such treatment must be carefully weighed against the potential morbidity of somewhat empirical technologies based upon limited animal experimentation. The current state of research and development suggests that the goal is best accomplished through a two-pronged approach involving (1) staged, pilot clinical research trials of therapeutic interventions, and on-line detection and prediction algorithms in humans and (2) basic research into the mechanisms underlying seizure generation and spread. Pilot studies of brain stimulation technology, partnering industry with academic centers in the United States, Europe and Canada are rapidly advancing our knowledge of how to implement implantable epilepsy devices. In particular, they are pointing out the potential technological pitfalls of such devices, and how to address problems associated with localization of specific targets, including the role of brain imaging and intraoperative neurophysiology, and how to measure outcome and adverse effects of this therapy and associated procedures. An MRI scan of a patient enrolled in such a trial is reproduced in Figure 2. At the same time, basic research into related work in engineering, neuroscience and computational modeling of neuronal networks will help improve targeting, timing and efficacy of clinical devices in an iterative fashion. While the ultimate goal of this research is to bring devices for epilepsy into the clinical realm as soon as possible, it is important that this desire be tempered by the need to understand the basic principals upon which therapy is predicated, at least to the degree that the potential for long-term side-effects, such as kindling of new epileptic foci, is understood.

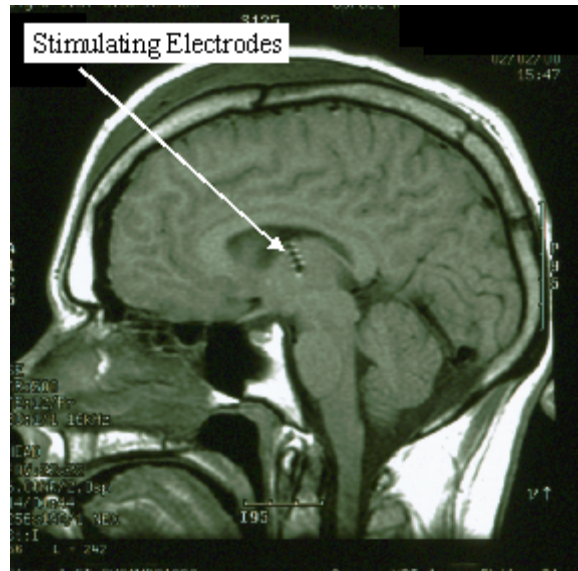


Figure 2: MRI of patient implanted with anterior thalamic nucleus stimulator for epilepsy.

It is not quite clear what kind of clinical trials and results will be required to stimulate acceptance of implantable devices for epilepsy. In the long run, double blind, controlled trials of sufficient power to demonstrate considerable efficacy will be required. While it is difficult to speculate just how effective these devices will need to be to gain acceptance, many investigators feel that they will need to demonstrate considerably more than then 10-12% seizure-free rate or 20-30% average reduction in number of seizures that are seen in most new seizure medications as they are brought to market. It seems natural to assume that in order to undergo intracranial surgery, though the potential morbidity and mortality are low, most individuals will require a substantial promise of being seizure free or nearly seizure free, in order to move forward, unless there is some other clear clinical benefit to the devices, such as stopping falls or seizure-related injuries. This would apply primarily to those individuals who have some control on medications, but continue to have enough seizures so that they cannot drive, and suffer significant negative impact on their quality of life. For those individuals with no other therapeutic options, even a small potential benefit may be adequate to consider an implant trial.

#### V. CONCLUSION

A convergence of new findings in biomedical engineering, clinical epileptology and neuroscience, coupled with keen interest from industry and a great clinical need are rapidly pushing technology for implantable devices to treat epilepsy forward. Development of better algorithms to detect and predict seizures is proceeding in parallel with new technologies to arrest seizures, both in vitro and in vivo. Early positive results of animal experiments, particularly

utilizing electrical stimulation, are forming the foundation upon which pilot human trials are based. Basic science research into the mechanisms underlying these therapies and their effects is also moving forward, although more slowly. Accepted and FDA approved cardiologic devices are providing models for the development of neurological implants, and experience with similar devices for Parkinson's disease, though not yet FDA approved, are accelerating development. Clinical performance standards for implantable devices for epilepsy will likely require greater efficacy than new antiepileptic drugs and the vagal nerve stimulator, due to the invasiveness of newer techniques. New techniques for seizure detection and prediction will likely enable individually trained, customized, intelligent devices which, though more complex than "blind" stimulating devices, may have the potential to demonstrate much greater efficacy in the long term, provided computational burden and the side effects of brain stimulation in the region of the epileptic focus are acceptable.

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#### VII. REFERENCES

- [1] W. Penfield and H. Jasper, *Epilepsy and the Functional Anatomy of the Human Brain*. Boston: Little Brown and Co., 1954.
- [2] K. Gale, "Subcortical structures and pathways involved in convulsive seizure generation," *J Clin Neurophysiol*, vol. 9, pp. 264-77., 1992.
- [3] L. Vercueil, A. Benazzouz, C. Deransart, K. Bressand, C. Marescaux, A. Depaulis, and A. L. Benabid, "High-frequency stimulation of the subthalamic nucleus suppresses absence seizures in the rat: comparison with neurotoxic lesions," *Epilepsy Res*, vol. 31, pp. 39-46., 1998.
- [4] M. A. Mirski, L. A. Rossell, J. B. Terry, and R. S. Fisher, "Anticonvulsant effect of anterior thalamic high frequency electrical stimulation in the rat," *Epilepsy Res*, vol. 28, pp. 89-100., 1997.
- [5] K. H. Tress and L. J. Herberg, "Permanent reduction in seizure threshold resulting from repeated electrical stimulation," *Exp Neurol*, vol. 37, pp. 347-59., 1972.
- [6] M. Mirski and R. Fisher, "Electrical stimulation of the mammillary nuclei increases seizure threshold to pentylenetetrazol in rats," *Epilepsia*, vol. 35, pp. 1309-1316, 1994.
- [7] A. A. Shandra and L. S. Godlevsky, "Antiepileptic effects of cerebellar nucleus dentatus electrical stimulation under different conditions of brain epileptisation," *Indian J Exp Biol*, vol. 28, pp. 158-61., 1990.
- [8] S. A. Chkhenkeli and I. S. Chkhenkeli, "Effects of therapeutic stimulation of nucleus caudatus on epileptic electrical activity of brain in patients with intractable epilepsy," *Stereotact Funct Neurosurg*, vol. 69, pp. 221-4., 1997.
- [9] R. S. Neuman, "Suppression of penicillin-induced focal epileptiform activity by locus ceruleus stimulation: mediation by an alpha 1-adrenoceptor," *Epilepsia*, vol. 27, pp. 359-66., 1986.
- [10] K. Morimoto and G. V. Goddard, "The substantia nigra is an important site for the containment of seizure generalization in the kindling model of epilepsy," *Epilepsia*, vol. 28, pp. 1-10., 1987.
- [11] J. Zabara, "Inhibition of experimental seizures in canines by repetitive vagal stimulation," *Epilepsia*, vol. 33, pp. 1005-12., 1992.
- [12] E. Fanselow, A. Reid, and M. Nicolelis, "Reduction of Pentylenetetrazole-Induced Seizure Activity in Awake Rats by Seizure-Triggered Trigeminal Nerve Stimulation," *Journal of Neuroscience*, vol. 20, pp. 8160-8168, 2000.
- [13] D. M. Durand and E. N. Warman, "Desynchronization of epileptiform activity by extracellular current pulses in rat hippocampal slices," *J Physiol (Lond)*, vol. 480, pp. 527-37, 1994.
- [14] B. Gluckman, H. Nguyen, S. Weinstein, and S. Schiff, "Adaptive Electric Field Control of Epileptic Seizures," *Journal of Neuroscience*, vol. 21, pp. 590-600, 2001.
- [15] M. W. Hill, M. Wong, A. Amarakone, and S. M. Rothman, "Rapid cooling aborts seizure-like activity in rodent hippocampal- entorhinal slices," *Epilepsia*, vol. 41, pp. 1241-8., 2000.
- [16] A. G. Stein, H. G. Eder, D. E. Blum, A. Drachev, and R. S. Fisher, "An automated drug delivery system for focal epilepsy," *Epilepsy Res*, vol. 39, pp. 103-14, 2000.
- [17] I. S. Cooper and A. R. Upton, "Effects of cerebellar stimulation on epilepsy, the EEG and cerebral palsy in man," *Electroencephalogr Clin Neurophysiol Suppl*, vol. 34, pp. 349-54, 1978.
- [18] M. Velasco, F. Velasco, A. L. Velasco, F. Jimenez, F. Brito, and I. Marquez, "Acute and chronic electrical stimulation of the centromedian thalamic nucleus: modulation of reticulo-cortical systems and predictor factors for generalized seizure control," *Arch Med Res*, vol. 31, pp. 304-15., 2000.
- [19] M. Velasco, F. Velasco, A. L. Velasco, B. Boleaga, F. Jimenez, F. Brito, and I. Marquez, "Subacute electrical stimulation of the hippocampus blocks intractable temporal lobe seizures and paroxysmal EEG activities," *Epilepsia*, vol. 41, pp. 158-69., 2000.
- [20] J. M. Van Buren, J. H. Wood, J. Oakley, and F. Hambrecht, "Preliminary evaluation of cerebellar stimulation by double-blind stimulation and biological criteria in the treatment of epilepsy," *J Neurosurg*, vol. 48, pp. 407-16., 1978.

- [21] R. Fisher, S. Uematsu, G. Krauss, B. Cysyk, R. McPherson, R. Lesser, B. Gordon, P. Schwerdt, and M. Rise, "Placebo-controlled pilot study of centromedian thalamic stimulation in treatment of intractable seizures.," *Epilepsia*, vol. 33, pp. 841-851, 1992.
- [22] R. S. Fisher and A. Handforth, "Reassessment: vagus nerve stimulation for epilepsy: a report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology," *Neurology*, vol. 53, pp. 666-9., 1999.
- [23] R. P. Lesser, S. H. Kim, L. Beyderman, D. L. Miglioretti, W. R. Webber, M. Bare, B. Cysyk, G. Krauss, and B. Gordon, "Brief bursts of pulse stimulation terminate afterdischarges caused by cortical stimulation," *Neurology*, vol. 53, pp. 2073-81., 1999.
- [24] B. Litt, R. Esteller, J. Echauz, M. D'Alessandro, R. Shor, T. Henry, P. Pennell, C. Epstein, R. Bakay, M. Dichter, and G. Vachtsevanos, "Epileptic Seizures May Begin Hours in Advance of Clinical Onset: A Report of 5 Patients," *Neuron*, vol. 29, pp. 51-64, 2001.
- [25] K. Lehnertz and C. Elger, "Can epileptic seizures be predicted? Evidence from nonlinear time series analysis of brain electrical activity," *Physical Review Letters*, vol. 80, pp. 5019-5022, 1998.
- [26] L. Iasemidis, K. Pappas, R. Gilmore, S. Roper, and J. Sackellares, "Preictal entrainment of a critical cortical mass is a necessary condition for seizure occurrence," *Epilepsia*, vol. 37, pp. (abstract), 1996.
- [27] M. Le Van Quyen, J. Martinerie, V. Navarro, P. Boon, M. D'Havé, C. Adam, B. Renault, F. Varela, and M. Baulac, "Anticipation of epileptic seizures from standard EEG recordings," *The Lancet*, vol. 357, pp. 183, 2001.
- [28] M. D'Alessandro, G. Vachtsevanos, A. Hinson, R. Esteller, J. Echauz, and B. Litt, "A Genetic Approach to Selecting the Optimal Feature for Epileptic Seizure Prediction," *IEEE International Conference on Engineering, Medicine and Biology, Istanbul, Turkey Submitted*, 2001.
- [29] H. Qu and J. Gotman, "A patient-specific algorithm for the detection of seizure onset in long-term EEG monitoring: Possible use as a warning device," *IEEE Transactions of Biomedical Engineering*, vol. 44, pp. 115-122, 1997.
- [30] I. Osorio, M. Frei, D. Lerner, and S. Wilkinson, "Automated rapid seizure detection in the human ECoG," presented at Eighth IEEE Symposium on Computer-Based Medical Systems, 1995.